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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/880,149	06/14/2001	John H. Kenten	2757-5	7213

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EXAMINER	
WINKLER, ULRIKE	

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 08/24/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/880,149	KENTEN ET AL.	
	Examiner	Art Unit	
	Ulrike Winkler	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *24-30,36,37,40 and 43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24-30,36,37,40 and 43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Request for Continued Examination

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on June 4, 2004 has been entered.

The Amendment filed May 4, 2004 in response to the Office Action of February 24, 2004 is acknowledged and has been entered. Claims 24-30, 36, 37, 40 and 43 are pending and are currently being examined.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Claim Rejections - 35 USC § 112

The rejection of claims 24-30, 36, 37, 40 and 43 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention **is maintained** for reasons of record.

Applicant's arguments have been fully considered but are not persuasive. Applicant's arguments are that "the E2 and E3 elements are well known to person of ordinary skill. The genome has been sequenced, and most of the E2 and E3 elements are available, either directly of via standard cloning methods to person of ordinary skill in the art." Knowledge of the structure

of the E2 or E3 element itself will not provide insight regarding the structure of the compound that binds to the E2 or E3 element. It is the compound binding to the E2 or E3 element that is being claimed in the instant invention. A review of the specification indicates that Applicants have exemplified a number of ubiquitin recognition elements, however, there appears to be no structural similarity between those elements. The specification also indicates that new ubiquitin recognition elements may be found using the methods set out in the specification (page 30, lines 1-3) providing further evidence that the structure of the ubiquitin recognition element is indeterminate.

The instant specification has not provided any compounds that achieve the method of reducing the level and/or activity of a target protein when the target protein is found inside a cell or when the cell is found inside a body. The instant specification has not provided any structure of a compound that can be used to treat a disease in an animal. This is analogous to the situation found in *Univeristy of Rochester v G.D. Searle & Co.*, 69 USPQ2d 1886 (CA FC 2004, see paragraph bridging 1894-1895) "...'850 patent does not disclose the structure or physical properties of any of the compounds required to practice the claimed methods, and that the structure of such compounds cannot be deduced from any known structure-function correlation". The instant specification and claims do not provide sufficient functional and structural characteristics of the ubiquitin recognition element or the ubiquitination system coupled with a known or disclosed correlation between function and structure. Since the disclosure fails to describe the common attributes or characteristics that identify members of the group comprising ubiquitin recognition element, the disclosure of particular compounds is insufficient to describe the genus of molecules, encompassed by the claimed invention. Therefore, there is lack of

written description in the instant invention for the claimed method of reducing the level of a protein inside a cell.

The rejection of claims 24 and 36 recites the limitation "the ubiquitination system" in the claim **is withdrawn** in view of Applicant's amendment to the claims in the amendment filed November 20, 2003.

New Rejection:

Claims 24-29 and 36-37, 40 and 43 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The instant claims are indefinite in the recitation of "method of reducing the level and/or activity of a target protein" because the nature and the therapeutic endpoint(s) of claimed methods are ambiguous and unclear. There is an absence or lack of clarity as to critical or resolutions steps or endpoints which reads back on the preamble of the claimed methods. Correction is required.

Claims 24-30, 36, 37, 40 and 43 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for ubiquitination of a protein using a compound in a cell lysate assay system, does not reasonably provide enablement for ubiquitination of a compound within a cell (claims 24, 25, 29, 36, 37 and 40) and for the use of the compound as a pharmacological agent in a patient (claims 26-28 and 30). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to

practice the invention commensurate in scope with these claims. Specifically the instant specification has not set out use the compounds for the purpose of reducing the level and or activity of a protein inside a cell. This rejection reinstates the enablement rejection made in the Office action mailed October 3, 2002. Applicant's prior arguments are addressed below.

The specification does not set forth sufficient teachings to allow one skilled in the art to use the claimed method of reducing the activity of a target protein by directing the protein to the ubiquitin degradation pathway using a compound within a cell or within a patient. (1) the nature of the invention is to bring a target molecule into close proximity to the ubiquitin conjugating enzymes so that the target molecule will be labeled with ubiquitin and subsequently be degraded. Issues of concern are availability of the compound to the ubiquitination system and the accessibility of the compound to cells within a patient.

(3) the presence or absence of working examples, the specification does not provide any working examples that would indicate the claimed compounds are able to enter a cell or be administered to an animal in such a way that they will be effective at targeting a protein to the ubiquitination pathway. The specification does not provide any evidence that the compound is taken up (absorbed) by a cell. There is no evidence that the compound is not degraded before it will reach the target cell and before it will reach the target protein destined for destruction. The specification provides experimental observation from cell-extracts using rabbit reticulocyte, HeLa cell and Jurkat cell lysate (examples 3 and 4). The specification has shown a compound that comprises a recognition element attached to fluorascein. Here the anti-fluorascin antibody is the target molecule for ubiquitin. Another compound is a recognition element conjugated to 4-aminophenyl arsenoxid.

Characteristics of a compound's activity *in vitro* using purified or partially purified components generally differs significantly with the compound when used on a whole cell. Additionally, cultured cell lines generally differ significantly from *in vivo* animal models. To be effective within a patient the compound must be delivered into the circulation in a sufficient concentration and for a sufficient period of time. *In vitro* assays cannot duplicate the complex conditions of *in vivo* therapy. In the *in vitro* cell-free assays, the compound is in constant contact with ubiquitination machinery. This is not the case *in vivo*, where exposure to the target may be delayed or inadequate. In addition, variables such as biological stability, half-life or clearance from the blood are important parameters in achieving successful therapy with the compound. The composition may be inactivated *in vivo* before producing a sufficient effect, for example, by proteolytic degradation or immunological activation. In addition, the composition may not otherwise reach the target because of its inability to penetrate tissues or cells where its activity is to be exerted, may be absorbed by fluids, cells and tissues where the composition has no effect, circulation into the target area may be insufficient to carry the composition and a large enough local concentration may not be established.

(4) the amount or direction or guidance presented, the specification provides evidence of using specific ubiquitination recognition elements which are chemically cross-linked with a target protein and show an increase in ubiquitination of the target protein under *in vitro* cell free experimental conditions. The specification does not provide sufficient guidance to allow one skilled in the art to use the claimed method of "activating" the ubiquitination activity directed to a target protein inside a eukaryotic cell which is the essential feature of the claimed invention. The specification does not provide teachings to establish effective dosages or methods of

administration of activating compounds. The specification does not provide any teaching as to how to administer the activating compounds to effectively treat an animal or human. No working examples are provided which would provide sufficient guidance to allow one skilled in the art to practice the embodiments of the invention with a reasonable expectation of success.

(5) the quantity of experimentation necessary, is high as it is not predictable that a compound will be taken up by the cells and that they will be available and active in the cytosolic environment of the cell where the ubiquitination enzymes are found. (6) the relative skill of those in the art is high. (7) the predictability or unpredictability of the art, the predictability based on the prior art is such that changing the N-terminal amino acid sequence of a protein would target a protein to the ubiquitin conjugating enzymes and once labeled these proteins will be degraded. The prior art lacks predictability in regards to the ability of the compounds to traverse the cell membrane and localize to the cytosol as well as being active within the environment of the cytosol. There is lack of predictability in the art as to the effect of a compound *in vivo* versus the effect of the same compound in an *in vitro* assay environment. (8) the breadth of the claims, the specification provides insufficient guidance with regard to the issues of binding affinity to the ubiquitination system, cellular uptake and availability and provides no working examples of *in vivo* experiments which would provide guidance to one skilled in the art. No evidence has been provided which would allow one of skill in the art to predict the efficacy of the claimed of activation compound of the ubiquitination system as treatment method. Without sufficient guidance the applicant is inviting the artisan to perform undue experimentation. Therefore the instant invention is not enabled for the broadly claimed method of activation of ubiquitination, treatment of disease and administering the compound to an animal.

Applicant's prior arguments from the response of March 3, 2003 are: (1) There are alternative methods for introducing molecules into a cell, citing electroporation or other physical methods. (2) Applicant's cite several papers regarding cell penetrating peptides and cargo delivery methods and the use of SNARE proteins to deliver DNA into a cell. (3) Issues of degradation were addressed by stating if the drug would not be degraded it would not be an ideal drug candidate as it would not be possible to reverse the actions of the drug. That degradation or elimination provides an important route to terminate treatment.

Upon review and reconsideration Applicants arguments are not convincing because the specification has not set out any teachings of how to use a compound to effectively treat a cell or a cell as it is found in a body which results in the degradation of a target protein. Citing the alternative methods of introducing a molecule into a cell does not overcome the shortcoming of the specification for failing to provide any evidence that would indicate the compound can be administered to an animal and will be able to function as claimed. The methods that the Applicants suggest such as electroporation would not work for the introduction of a molecule into a cell that is found within an animal. The use of cell penetrating peptides or SNAREs would require the addition of these peptide to the compound which is made up of a ubiquitination element and a target binding protein. There is no indication in the specification that peptides can be added to the compound without effecting the binding affinity of the compound to the target binding protein or the binding to the ubiquitination element. Therefore, Applicant's arguments that peptides can be used for the introduction of molecules into a cell (citing several references) is not convincing because there is no evidence in the specification that other molecules can be added to the compound. The statement that degradation or elimination provides an important

route to terminate the treatment does not address the failing of the specification to teach a compound that can be used in the claimed method that will function to effectively decrease the level and/or activity of a target protein in an animal.

Therefore, it remains the Offices position that the instant specification is not enabled for the use of a compound to reduce the level of a target protein within a cell or within an animal.

Conclusion

No claims allowed.

Papers related this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG (November 15, 1989). The Group 1600 Official Fax number is: (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Tech Center representative whose telephone number is (571)-272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ulrike Winkler, Ph.D. whose telephone number is 571-272-0912. The examiner can normally be reached M-F, 8:30 am - 5 pm. The examiner can also be reached via email [ulrike.winkler@uspto.gov].

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached at 571-272-0902.

ULRIKE WINKLER, PH.D
PRIMARY EXAMINER 8/20/04